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14. ABSTRACT

The purpose of this study is to investigate mechanisms of disequilibrium and imbalance in veterans of Operation Enduring Freedom / Operation Iraqi Freedom who have experienced traumatic brain injury (TBI). The mechanism of chronic dizziness and imbalance after TBI is not known. The hypothesis for this study is that TBI leads to an impairment in the vestibular reflexes that compensate for linear movements of the head and body during standing and walking. The experimental protocol has two parts. First, we use an infrared motion-tracking system to record the movements of the body during balance and walking tasks. Then, we use eye movement recordings during linear and rotational motion to perform a comprehensive assessment of the vestibular reflexes. Data recorded in veterans with a history of TBI are compared to those from neurologically normal control subjects who report no balance problems. We have recorded data from veterans with TBI and control subjects, and we continue to recruit additional subjects. To date, we have found significant TBI-related deficits in vestibulo-ocular reflexes, as well as in static and dynamic postural control, and locomotion.

15. SUBJECT TERMS
Traumatic brain injury, balance, locomotion, vestibular, eye movements

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INTRODUCTION

The objective of this study is to investigate mechanisms of balance impairment in veterans of Operation Enduring Freedom / Operation Iraqi Freedom (OEF/OIF) who have experienced traumatic brain injury (TBI). Persistent disequilibrium is a known post-concussive symptom, and recent surveys of veterans have confirmed that this is also true of blast-related mild TBI (Cave et al. 2007; Scherer et al. 2007; Scherer and Schubert 2009). Prior studies in civilians have documented objective impairments in balance and locomotion after TBI, but detailed studies have not been conducted following combat-related TBI, and it is not known whether blast injuries produce balance deficits that are similar to those that occur after blunt TBI in civilians. Moreover, in neither group has the relationship of these deficits to vestibular injury been adequately explored. Specifically, little is known about the effect of blast-exposure and TBI on the reflexes derived from the otolith organs of the vestibular labyrinth (the organs that respond to linear motion and sense gravitational acceleration). These reflexes are likely to be of particular importance for balance and equilibrium. The hypothesis of this study is that impaired otolith reflexes account for persistent dizziness and gait impairment after traumatic brain injury. We are testing this hypothesis in a series of experiments designed to measure directly the otolith- and canal-mediated vestibulo-ocular reflexes and to correlate these to quantitative measures of static and dynamic balance and of walking. The results of this study will not only provide critical information regarding the pathophysiologic mechanisms of balance impairment after TBI, but they will also facilitate improved diagnosis of these problems in the acute and chronic settings.

This report represents the third year of this study. A no-cost extension has been requested for an additional year, to complete the work, and is expected to be approved.

BODY

TASK 1: VOR Measurements

This task addresses Specific Aim 1: <u>Are vestibulo-ocular reflexes impaired in TBI subjects with disequilibrium</u>? To test this hypothesis, we compare eye movements during translational head motion (the translational vestibulo-ocular reflex, tVOR) between control and TBI subjects. Measurements are performed on our Moog motion platform using scleral coils or video-oculography to record eye movements. Responses to horizontal and vertical linear translations and to horizontal rotations are recorded. Our hypothesis predicts a specific deficit in translational vestibular responses, i.e. eye movements evoked by stimulation of the otolith organs.

So far, we have recorded data from seven subjects with TBI and ten normal subjects; we also have data from a much larger group of normal subjects from prior studies. In this study, we test the tVOR in response to both abrupt and sinusoidal (2 Hz) motion. We quantify the tVOR by its "gain," the ratio of measured ideal eye velocity to the ideal velocity that would stabilize the eyes on the target of regard. Full gaze stabilization occurs when the gain is 1 (eye velocity is equal to the ideal). As shown in Figure 1 (Appendix), as a group subjects with mTBI have lower gains in response to 2 Hz translation than do normal subjects ($p < 0.02$). This supports our hypothesis that combat mTBI can result in impaired dynamic otolith function.

One challenge in interpreting the tVOR is emerging as we explore the responses of normal subjects in our laboratory. Recent findings indicate that cognitive and predictive mechanisms are likely to play a non-trivial role in the responses to sustained predictable motion, such as the 2 Hz translations that are a part of this study. Given this, compensatory or predictive components could mask or reduce apparent primary otolith deficits in some subjects. We are addressing this issue by examining the initial responses to 2 Hz and step translations (before prediction has an opportunity to develop) and by recording responses to less predictable motion (sum-of-sines stimuli). In a small report based on analysis of responses in several normal subjects, we showed that sum-of-sines responses are different from those to 2 Hz motion and thus may be better able to detect otolith deficits (Walker and Liao 2011, Appendix 4). We continue to analyze responses during the initiation of 2 Hz translation; preliminary results (as reported in the June 2011 quarterly report) suggested that responses during this phase (that may more closely measure primary otolith function) are also lower in mTBI subjects. In the next year, we will complete analysis of the early tVOR and examine sum-of-sines tVOR responses in those subjects in whom they have been recorded. We will also compare these tVOR gains with balance measures (Task 2) across subjects to test the hypothesis that a greater impairment of dynamic otolith function, as measured by the tVOR, is associated with greater postural instability.

As we have previously discussed, there are several reasons why tVOR gains may not be closely correlated with balance measures, even if impaired otolith-spinal reflexes contribute to disequilibrium in these veterans. First, it may be that our attempts to isolate vestibular function within the tVOR (e.g., focusing on responses to initial motion) may still not adequately exclude predictive and other cognitive components. Second, it may be that vestibulo-ocular reflexes are not affected in the same way as the vestibulo-spinal reflexes that control balance. Third, it is possible that balance deficits are multifactorial after TBI, consisting of a combination of vestibular dysfunction and other motor control abnormalities, and that the

relative contribution of these components may differ among individuals. Finally, since we are often unable to study veterans near to the time of injury, it may be that partial recovery and adaptation processes that have already occurred are obscuring the extent of a vestibular injury in some cases. Compensation of the tVOR could occur differently from that of vestibulo-spinal function.

Regardless of these challenges and the variability of the responses, our results so far nonetheless support a deficit in dynamic otolith-ocular reflexes after combat mTBI, a new and important finding. This at least suggests that vestibular impairment may be an important contributor to imbalance in some, if not all, TBI cases.

TASK 2: Balance and Gait Assessment

This task is performed in tandem with Task 1. Its purpose is to define precisely the gait and balance deficits associated with mTBI and then to relate them to our measures of the tVOR. Each subject in whom we record vestibular responses also undergoes detailed testing of gait and balance function. In the past year, data from additional subjects and ongoing data analysis have confirmed and solidified our previously reported preliminary findings. So far, we have found impairments associated with mTBI in all areas studied: static posture (quiet standing), dynamic posture (responses to sudden pulls of the trunk with unpredictable timing), and gait.

Static Balance

Body kinematics and surface EMG of leg muscles are recorded while subjects stand quietly and as still as possible on firm (force plate) and compliant (10cm thick foam) surfaces, with eyes both open and closed. In the past year, we have made considerable progress in the analysis of these data. Using an infrared motion tracking system, we have found that mTBI subjects have decreased postural stability (more body motion) in all conditions, but especially when the eyes are closed and when standing on foam (Figure 2, Appendix 1). Standing on foam with eyes closed is likely to be most dependent on vestibulo-spinal reflexes, because the contribution of vision to balance is eliminated and that of proprioception is minimized. Although this does not directly prove that deficient otolith function causes imbalance after mTBI, it is nonetheless strongly supportive of our hypothesis. Both the displacement from the start position (Figure 3, Appendix 1) and the total amount of sway, as measured by sway path length (Figure 3, Appendix 1), are significantly increased in our mTBI subjects with disequilibrium. A linear model shows significant effects not only of the subject group (TBI vs no TBI) but also of standing surface (worse on foam) and eye closure (see Figure 4 legend for details).

Given that the length of the sway path is increased in the mTBI group, it is expected that the average sway speed will also be greater. An interesting, and non-trivial finding, however, is that sway speed was increased beyond what would be predicted by postural displacement (Figure 5, Appendix 1). Thus, an increased sway speed cannot simply be explained by a larger excursion of sway from the center position. Subjects move more and faster, even when the range is small. This finding provides further evidence for a deficit in dynamic postural control. We will examine EMG data from these recordings for possible insight into the nature of this deficit.

Dynamic Balance

Dynamic postural control is tested by recording subjects' responses (body kinematics and surface EMG) to abrupt perturbations delivered by a computer-controlled linear actuator through a rope attached to a belt around the waist. Although the direction is known, the timing is not predictable. We determine the onset of the pull using the acceleration of the sacral marker and then determine the amount of trunk motion (both maximum displacement and the total path length) for a fixed time from pull onset. We have found both qualitative and quantitative differences between the mTBI group and control subjects without TBI. Qualitatively, the nonTBI subjects tend to have more consistent responses from trial to trial (less variability), both in terms of path traveled and timing. Quantitatively, the overall path length is longer in mTBI subjects than in control subjects, for both forward pulls (dependent largely on the sacculus) and lateral pulls (dependent on the utriculus). Although there was some variability, by multivariate ANOVA there was a significant effect of group on path length ($p < 0.001$).

Gait Speed and Stability

As we have already reported, mTBI subjects walk more slowly and with greater lateral sway than do control subjects without TBI. Our current efforts are to extend this analysis to examine more specifically gait kinematics and limb segment coordination during walking. This will be a major effort of data analysis in the no-cost extension period.

In summary, our findings continue to support the hypothesis that veterans who have experienced mTBI and who report disequilibrium have distinct objective balance and locomotion deficits that affect both static and dynamic postural control. The specific findings (e.g., balance deficits that are accentuated by eye closure and by standing on a compliant surface) match what would be expected in the setting of vestibular impairment.

TASK 3: VOR Adaptation / Motor Learning
Due to the challenges in subject recruitment and the need for additional analysis of data from the primary study objectives, we have proposed to defer this third aim to future work, as indicated in the revised Statement of Work.

Challenges to the Project .

The main challenge to the work thus far has been subject recruitment. Although we see a large number of OEF/OIF veterans in our facility with a history of TBI, we have discovered that many are not interested in participating in our research studies. We have also had several subjects who initially expressed interest but then later changed their minds and decided not to enroll. As we have previously reported, we are addressing this recruitment challenge in two ways. First, some subjects have declined to participate or have been unable to complete testing due to an unusual eye sensitivity, such that they are unable to tolerate the scleral contact lens coils that we use to record eye movements. The cause of this sensitivity is uncertain but it is similar to the photophobia that these individuals also often have. To

accommodate this problem, we have obtained, tested, and implemented a high-speed video-oculography system to allow for non-invasive recording of eye movements. Second, in order to publicize our study more widely to additional veterans who may be interested in participating but not have otherwise heard of the study, we have obtained approval from our IRB, in conjunction with another CDMRP-sponsored TBI study based at the Cleveland Clinic (Stephen Rao, PI), to contact OEF/OIF combat veterans in the Cleveland area first by letter and then by telephone, to inform them of our studies and offer the opportunity to participate. We have at least several thousand local OEF/OIF veterans.

We have applied for, and anticipate receiving, a one-year no-cost extension to allow us to enroll more subjects, to complete data analysis, and to submit manuscripts for publication. The modified Statement of Work to include this no-cost-extension period is attached in Appendix 2.

Personnel Changes

In the last annual report, we indicated that Dr. Tao Pan, PhD, had been hired to replace Dr. Ke Liao as primary project engineer. Shortly thereafter, all human research approvals were completed, and he has assumed full responsibility for the project. He plays a major role in both the experimental and data analysis and software development aspects.

This month, Dr. Janis Daly, co-investigator and co-Director of the Motion Study Laboratory, has left the Cleveland VAMC to assume a new position as Director of the Brain Rehabilitation Center at the Gainesville, FL, VAMC. Although she is no longer in Cleveland, she will continue to be a consultant on the project. An engineer in her laboratory, Ms. Kristen Roenigk, was also supported part-time by the project. With the dissolution of the Daly group, she also has left the Cleveland VAMC. Dr. Pan has fully learned all of the experimental techniques (for gait and balance testing) as well as the associated data analysis, and he has assumed the tasks for which Dr. Roenigk was previously responsible. Thus, these changes will not impact our ability to complete the proposed work of this project.

KEY RESEARCH ACCOMPLISHMENTS

Although we have not completed recruitment and data analysis, key findings have already emerged from this work. These include:

- For the first time, we have successfully recorded ocular responses to translational motion in veterans with TBI. The data support our hypothesis that mTBI can lead to disruption of otolith-mediated vestibular reflexes.

- In detailed analysis of our data, we have found consistent gait and balance deficits after TBI. These include reduced gait speed and decreased static and dynamic postural stability while standing and walking. Postural stability is particularly impaired under conditions (eye closure, standing on a compliant surface) where vestibular input is expected to be most critical.

REPORTABLE OUTCOMES

Although we are still recruiting subjects, our results have already include a number of specific findings, outlined above, related to the tVOR and postural control after mTBI. Some of these findings are scheduled to be reported at a NATO-sponsored symposium during the first week of October (see Appendix 3 for abstract). We have also already begun to organize our key findings into manuscript form, but the finalization and submission of these manuscripts will be deferred until all data have been collected and analysis completed, within the next year. A short paper was published describing normal subjects' responses to unpredictable (sum-of-sines) motion (Walker and Liao, 2011).

CONCLUSION

This study will provide critical new information regarding the effect of TBI on vestibular function and the relationship of vestibular impairment to gait and balance problems. New data and additional analysis in the past year have confirmed our initial findings of specific balance and walking disturbances in veterans with TBI, encompassing both static and dynamic postural control. The findings are particularly noteworthy, considering that this group of veterans is young and has undergone extensive physical training as a part of their military service and thus would be expected to have exquisite balance and locomotion. As predicted, the balance deficits are greater in a more challenging task, such as standing or walking on foam, a condition in which a greater reliance on vestibular mechanisms is expected. Further data are required to assess the overall relationship between balance and the TVOR.

Our study will provide key information regarding the nature and mechanisms of combat-related traumatic injury. We anticipate that it will lead to improved diagnostic techniques for assessing functional impairment related to vestibular injury (which could be important for determining a veteran's capacity for performing duties that may depend on robust balance) and that it will help to improve and refine rehabilitative strategies for this important problem.

REFERENCES

Cave KM, Cornish EM and Chandler DW. Blast injury of the ear: clinical update from the global war on terror. *Mil Med* 172: 7: 726-730, 2007.

Scherer M, Burrows H, Pinto R and Somrack E. Characterizing self-reported dizziness and otovestibular impairment among blast-injured traumatic amputees: a pilot study. *Mil Med* 172: 7: 731-737, 2007.

Scherer MR and Schubert MC. Traumatic brain injury and vestibular pathology as a comorbidity after blast exposure *Phys Ther* 89: 9: 980-992, 2009.

Walker M and Liao K. The human translational vestibulo-ocular reflex in response to complex motion *Ann N Y Acad Sci* 1233: 1: 242-248, 2011.

APPENDIX 1: FIGURES
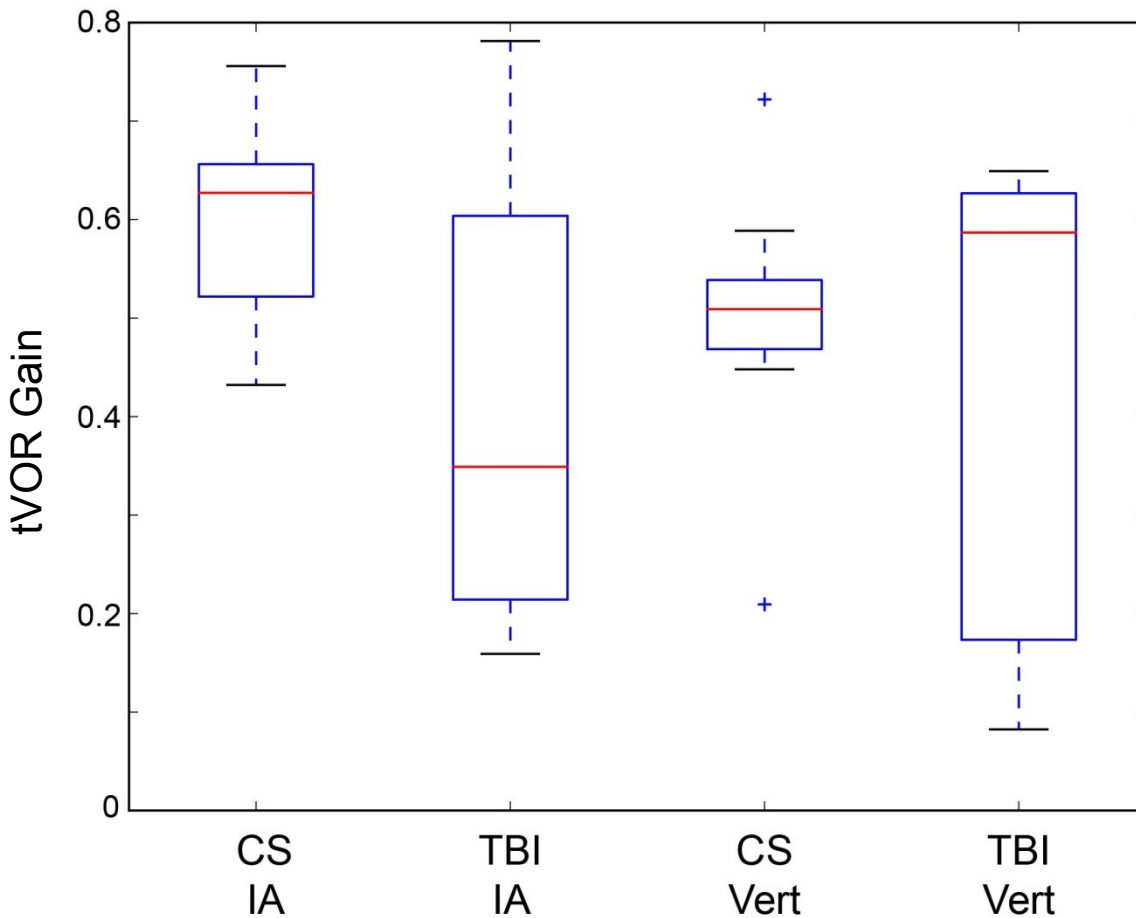
FIGURE 1: tVOR gains are lower in mTBI subjects. Gains (ratio of peak eye velocity to peak ideal eye velocity) for the translational vestibulo-ocular reflex (tVOR) in response to interaural (IA) and vertical (Vert) head motion. Data from nonTBI control subjects (CS) and from TBI subjects (TBI) are shown. Based on ANOVA (glm in R, log(gain) ~ subject group + motion direction), the groups are significantly different ($p < 0.02$) but the motion direction (interaural vs. vertical) is not ($p>0.3$). These results support an impairment of dynamic otolith reflexes to both horizontal and vertical motion after mTBI.
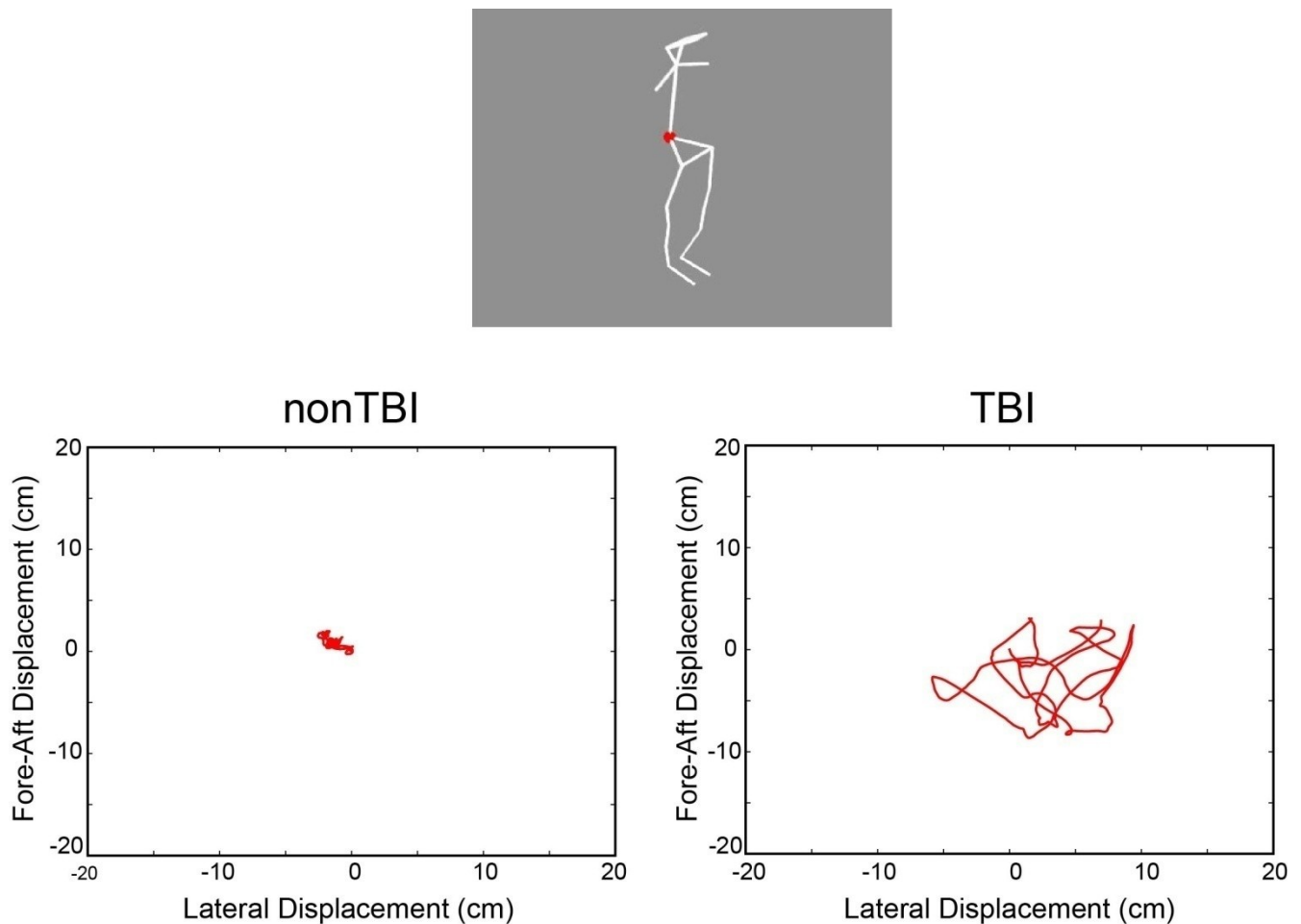
FIGURE 2: A TBI subject has more postural sway during quiet standing. Two-dimensional plots of pelvis (sacral marker) motion from the starting position during the first five seconds of the trial. Data from one control subject and one TBI subject are shown. The cartoon at the top depicts the positions of the markers on the body; the nodes connecting individual line segments are the marker positions. The sacral marker position is shown in red; quantitative data analysis was based on this marker, an estimate of the motion of the body's center-of-mass.
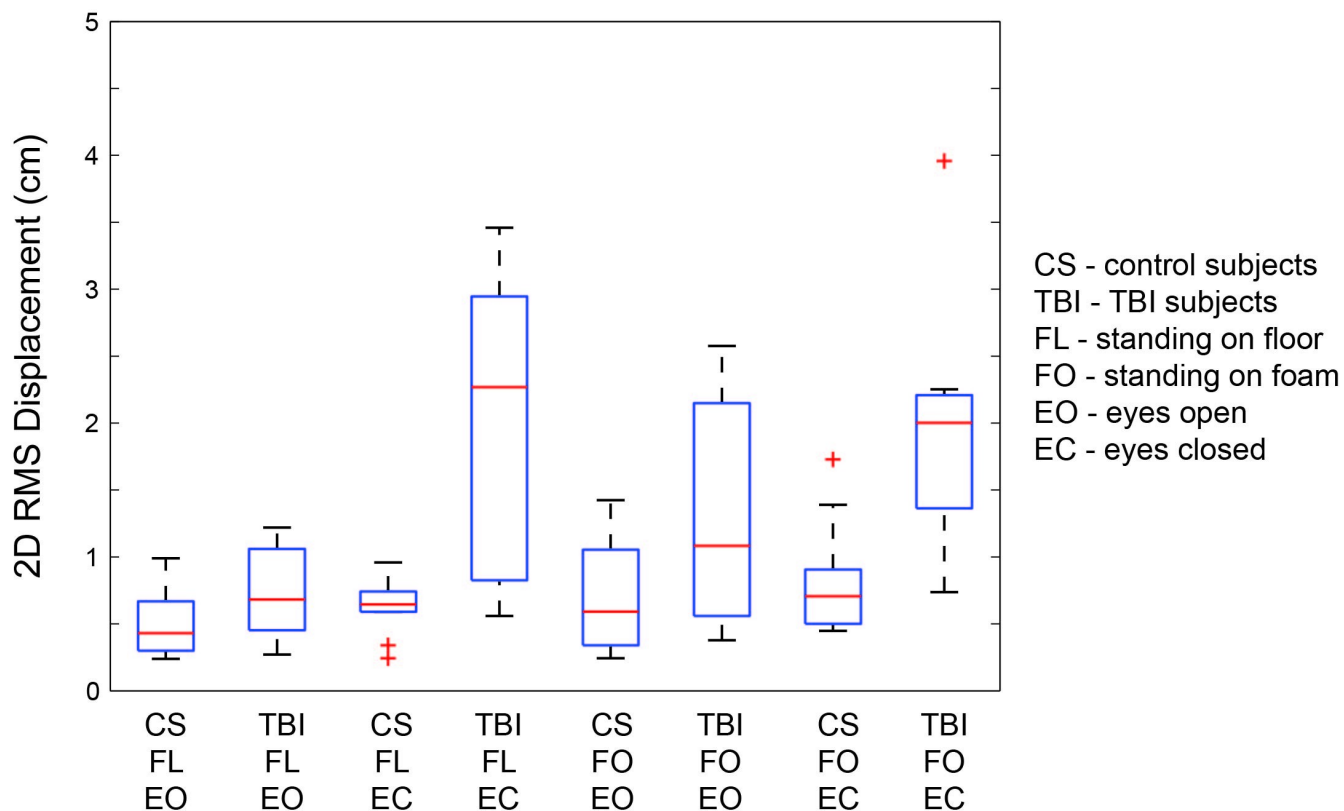
FIGURE 3: As a group, mTBI subjects have more postural sway while standing, especially with eyes closed. Two-dimensional (vector magnitude) RMS displacement of the pelvis (based on sacral infrared marker) during the first 5 seconds of recording for both nonTBI control subjects and mTBI subjects under all conditions (floor vs. foam, eyes open vs. eyes closed). Larger displacements indicate an increased range of sway. mTBI subjects have an increased range of sway with the eyes closed on both surfaces, but also with the eyes open on foam (perhaps due to decreased efficiency of proprioceptive input to contribute to balance). Based a linear model (log(Displacement) ~ Subject Group + Standing Surface + Eyes Open vs. Closed), the difference between groups ($p < 10^{-5}$) and between eyes open vs. closed ($p < 0.002$) were both significant (ANOVA). Whether subjects were standing on a firm or compliant surface had less effect than eye closure on balance. Although some mTBI subjects did worse on foam than on the floor with eyes open, the effect of standing surface did not reach significance ($0.05 < p < 0.06$).
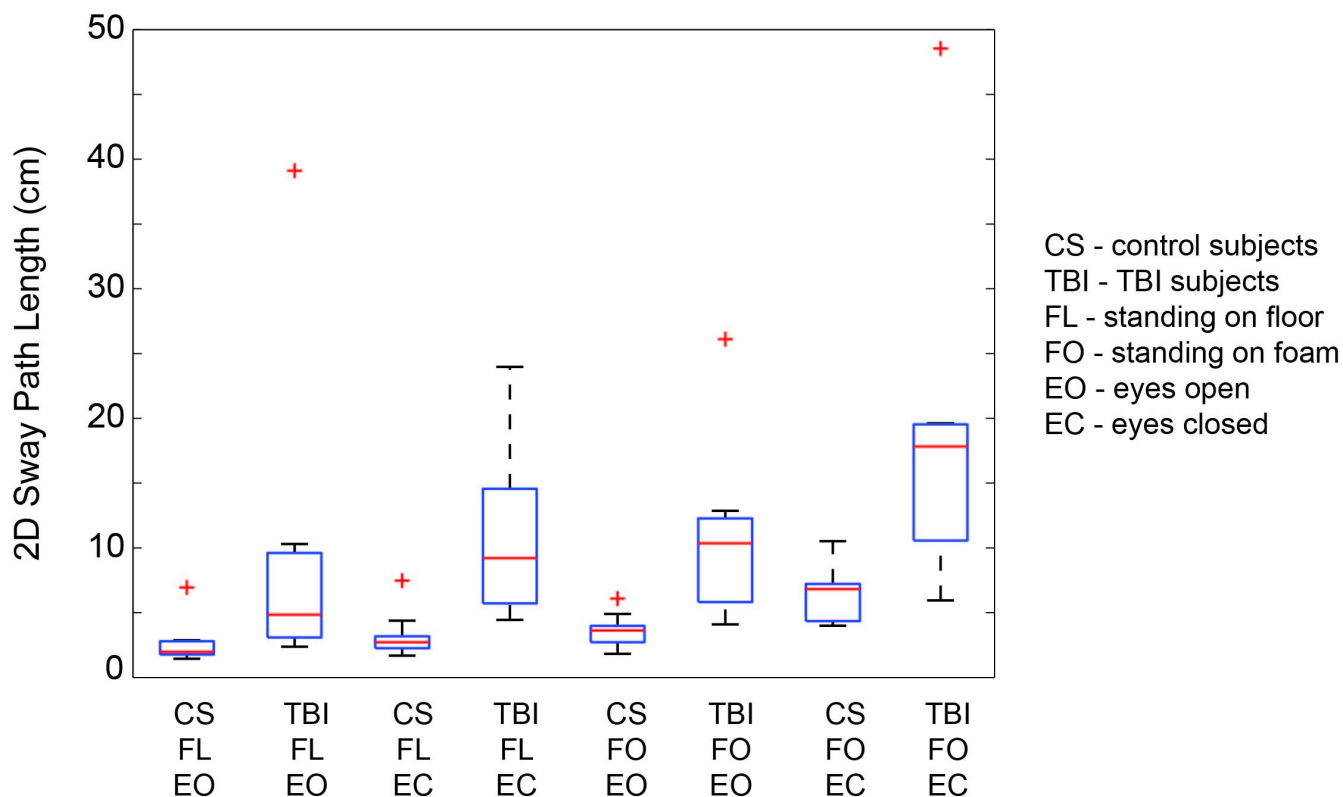
FIGURE 4: mTBI subjects have longer sway path lengths under all standing conditions. Boxplot of sway path length in two-dimensions for both groups and each standing condition (floor vs. foam, eyes closed vs. eyes open) for the first 5 seconds of recording. The red lines show the median values, the blue boxes the middle quartiles, and the whiskers the full range of the data, excepting outliers (shown in red). TBI subjects have greater path lengths (less postural stability in all conditions). The sway path length of TBI subjects in the easiest condition (standing on the floor with eyes open) is comparable to that of the control subjects in the most challenging condition (standing on foam with eyes closed). Based a linear model (log(Path Length) ~ Subject Group + Standing Surface + Eyes Open vs. Closed), the difference between groups was highly significant ($p < 10^{-9}$). The standing surface ($p<0.0002$) and eye closure condition ($p<0.001$) were also significant.
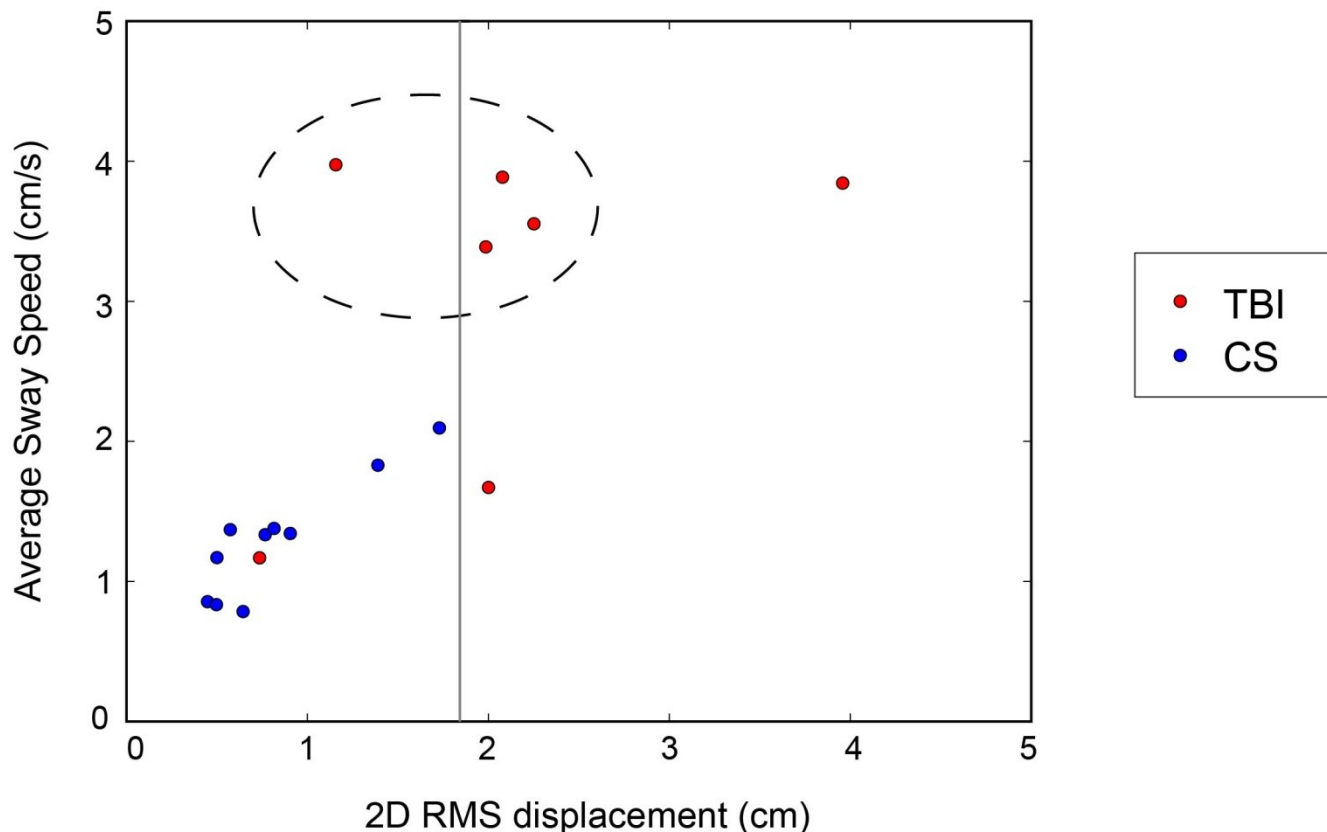
FIGURE 5: **Sway speeds are also increased in mTBI subjects.** Average 2D sway speed vs. 2D RMS displacement of the pelvis (based on sacral infrared marker) during standing on foam with eyes closed for control subjects without TBI (blue) and TBI subjects with disequilibrium (red). Using a linear model similar to those applied to displacement and length data, sway speeds were also significantly different for group, surface, and eye closure. Two additional findings are apparent from this scatter plot. First, 5/7 TBI subjects have sway displacements outside the range of the nonTBI subjects (those to the right of the gray line). These are the individual data contributing to the results of Figure 3. Second, 4/7 TBI subjects (within dashed ellipse) have much larger sway velocities for a given RMS displacement than do nonTBI subjects. This implies that there is less postural stability within the same postural range, a finding that provides further support for an impairment of dynamic postural control in these subjects.

APPENDIX 2: REVISED STATEMENT OF WORK

This revised Statement of Work outlines the work that we expect to have completed for the entire project by the end of the no-cost extension period; it incorporates what has already been accomplished. The primary change to the original SOW is the elimination of Task 3, a small pilot study of the adaptability of the vestibulo-ocular reflex after mTBI. This aim will be deferred to a future project, in order to focus our attention on completion of the primary objectives of this study. A few additional analyses have been added, as well as a new method of eye movement recording.

This study will be conducted in two coordinated sets of experiments in the same subject, each of which addresses one of the two primary specific aims. All work will be performed at the Louis Stokes Department of Veterans Affairs Medical Center (LSCDVAMC), 10701 East Blvd., Cleveland OH 44106.

All experiments use human subjects; no animal experiments are included. All work is conducted under a single human subjects' protocol, under approval of the Institutional Review Boards of the LSCDVAMC and University Hospitals – Case Medical Center, as well as the Human Research Protection Office of the U.S. Army Medical Research and Materiel Command.

TASK 1: VOR Measurements (AIM 1):

Measurements of the VORs are performed in the Daroff-Dell'Osso Ocular Motility Laboratory, on the Moog 6DOF2000E motion platform. The PI (Dr. Walker) supervises these experiments. The study engineer plays a central role in the conduct of experiments and analysis of data.

Experimental Methods: Three groups of subjects will be enrolled: (1) veterans with TBI and disequilibrium, (2) veterans with TBI but no dizziness, (3) normal subjects with neither TBI nor dizziness. The VORs are tested in a single experimental session using three motion stimuli: (1) yaw (horizontal) rotation at 1 and 2 Hz and in response to manual head rotations (head impulses), (2) interaural (side-to-side) translation, and (3) vertical translation. Translation is tested in response to both predictable (2 Hz) and unpredictable stimuli. Eye movements are recorded in a magnetic field search coil system with binocular scleral eye coils or with a binocular video-oculography system (I-SCAN). We have switched to video-based eye movement recording because some TBI subjects have ocular sensitivity that precludes them from wearing the scleral coils. Head motion is measured using a Vicon motion system with infrared reflective markers. Eye coil signals are digitized and saved on computer for later analysis.

Analytical Methods: Analysis is conducted using custom MATLAB™ and Python programs that have been written by the PI, study staff, and other members of the laboratory. The PI has extensive experience in MATLAB™ programming and in the analysis of eye movements and the VORs. For subjects tested with scleral coils, coil signals are converted to rotation vectors to determine eye movements. Video data are calibrated using a standard behavioral technique. The VORs are quantified by gain and gaze velocity. For each motion stimulus, the peak gaze velocity (eye velocity relative to target being viewed) is calculated and normalized to the peak ideal eye velocity. This *normalized gaze velocity* (NGV) is an inverse measure of the integrity of the VOR in question: an NGV of zero is a perfect response, and an NGV of 1 is no response.

Time frame: Analysis programs are written, and we have completed the majority of the analysis of data for the individual subjects that have already been tested. Data from newly

recruited subjects will be analyzed as they are acquired. Group and statistical analyses will be finalized when recruitment is complete.

<u>Outcome</u>: This experiment tests our hypothesis that vestibular reflexes are impaired in TBI subjects with dizziness, and it will provide important data on the pattern of that vestibular injury with respect to otolith and canal inputs. This information will then be available to guide development of more specific diagnostic and screening tests for TBI-related vestibular damage.

TASK 2: Gait and Balance Measurements (AIM 2):

Locomotion and balance are tested in the Motion Study Laboratory of the Functional Electrical Stimulation Center at the LSCVAMC. This laboratory is immediately adjacent to the Ocular Motility Laboratory, where VOR testing will be performed. Dr. Daly and her engineer, Ms. Roenigk, have assisted with the setup, conduct, and supervision of the gait and balance portion of the study. The engineer for this study, Dr. Pan, is now fully trained in the acquisition and analysis of these data.

<u>Experimental Methods</u>: Gait is recorded with the Vicon motion system, while the subject walks along a 10 m level walkway, first unobstructed, then on a compliant foam surface, and finally with four obstacles 12 inches above the ground and placed at 2 m intervals. For each condition, 10 trials are collected. Balance is assessed while the subject stands quietly (*static balance*), in light and darkness, on two surfaces: floor and foam; during voluntary side-to-side and front-to-back weight shifts (*active dynamic balance*); and after abrupt perturbations (*passive dynamic balance*).

<u>Analytical Methods</u>: Two measures are used to quantify gait, based on prior studies of TBI: (1) walking speed, and (2) lateral motion of the body's estimated center of mass (COM). Balance will be assessed by determining the motion of the body's COM (from Vicon data) and center of pressure (from force plate data), under the static and dynamic conditions. The statistical analysis, including the development of the model to relate gait to vestibular function, will be performed with the assistance of the Case Statistical Consulting Center.

<u>Time frame</u>: This experiment is conducted concurrently with Task 1, in the same time period. The same subjects will participate in both experiments, since one goal of the study is to relate gait and balance to vestibular function. Most of the analysis programs for this task have already been written and thoroughly tested, and individual data from subjects that have been studied thus far have been processed. During the final year of the study, we will prepare and submit manuscripts based on these results.

<u>Outcome</u>: This experiment will provide important new information regarding gait and balance deficits after TBI and their relationship to vestibular dysfunction. Unlike prior studies, we will include TBI subjects without dizziness to determine if gait deficits are only found in the context of subjective dizziness, or whether they are a more nonspecific consequence of TBI. Our study will also focus on a new and critical TBI population: veterans with combat-related TBI, often due to blast injuries. This will allow us to assess whether gait and balance effects are similar to, or different from, those measured in prior studies of blunt head trauma. Again, this task will not result in specific deliverable products, but it will provide information that can be used to develop better diagnostic, prognostic, and treatment tools.

## WORK TO BE DONE DURING NO-COST EXTENSION PERIOD

Although not complete, we have made considerable progress with this study. An additional year will allow us to record several more subjects, to finish the data analysis, and to prepare and submit manuscripts for publication. The following specific issues will be covered by the extension:

1) Recruitment: As we have outlined in progress reports, subject recruitment has been more challenging than we anticipated. We are addressing this issue in two ways. First, we found unexpectedly that subjects in this study (particularly those with mTBI) have had more difficulty tolerating the contact lens coils that we use for eye movement recordings, or they do not want to try to wear them. To address this, we recently acquired a video eye tracking system for our motion platform. This has already been implemented, and we have used it successfully to record VOR data. In addition, in conjuction with another USAMRMC-funded study to Dr. Stephen Rao, we are implementing a new method to publicize our study among all OEF/OIF veterans in the Cleveland area. We anticipate that this will allow us to identify eligible veterans who would like to participate but would otherwise not have known about the study.

2) Data analysis: Another year of support will allow us to complete analysis of data from current and additional subjects. Although our study was based on prior work, some of the specific tests employed were new and required development of new analysis tools and custom adaptation of others. The PI and study engineer, who have considerable experience in programming and data analysis, have invested substantial effort in development of computer programs to analyze the data from our study. Most of this is now complete; the additional time will be devoted to refining the methods and processing remaining data. Because the bulk of the data analysis is done on an individual subject basis, this can be done concurrently with the recording of the final subjects.

3) Publication and presentation of results: Several important findings have already emerged from the subjects that have been studied and the analysis that has been completed thus far. For example, we have found that veterans with a history of mTBI have specific impairment of standing balance and slowed and less stable walking. Some of these results will be presented at a NATO-sponsored meeting in Halifax in October. As we complete data analysis, we will prepare and submit at least three manuscripts for publication, addressing: 1) static and dynamic posture control, 2) gait stability, and 3) vestibular reflexes.

PROPOSED TIMELINE FOR NO-COST EXTENSION PERIOD
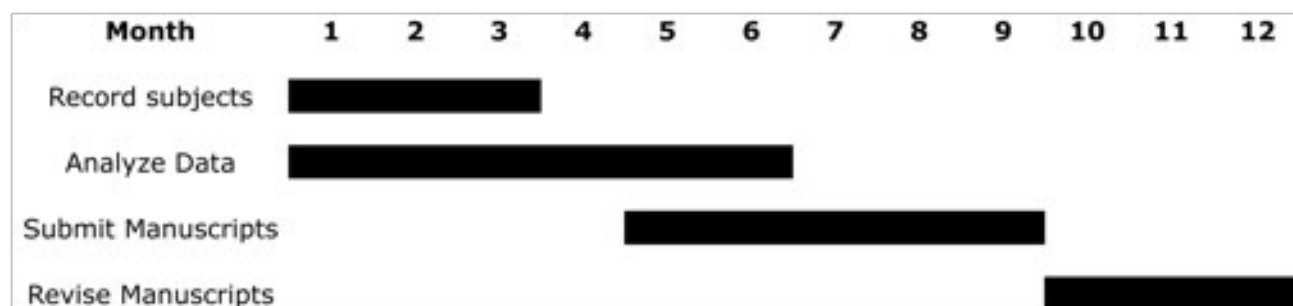
POSTURAL INSTABILITY IN BLAST-EXPOSED VETERANS

Mark Walker, M.D., Associate Professor of Neurology
Ke Liao, Ph.D., Research Associate
Tao Pan, Ph.D., Engineer
Kristin Roenigk, M.S., Engineer
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Topic: Blast-related neurotrauma

Introduction: Dizziness and imbalance are common in post-concussive syndrome after blunt head trauma and have also been reported in service members with mild traumatic brain injury (mTBI) due to explosions. Quantitative assessments are limited, particularly in the military population, and the mechanism of balance impairment is poorly understood. We hypothesize that balance deficits are due to concussion-related vestibular injury, either to the labyrinths or to central vestibular structures (e.g., cerebellum).

Rationale: The purpose of this study was to measure postural stability in veterans with mTBI and disequilibrium in comparison to healthy subjects without dizziness, focusing on conditions (eyes closed, standing on a compliant surface) that are most challenging to the vestibular system.

Methods: Seven OEF/OIF veterans with a history of mTBI and persistent disequilibrium and five healthy volunteers without a history of blast exposure were studied. A motion tracking system was used to record leg and trunk kinematics during quiet standing on a hard floor and on a foam surface, both with eyes open and closed. Postural stability was quantified by calculating body sway (root-mean-square (RMS) displacement in two dimensions) at the waist (sacral marker) and neck (marker at C7), and by calculating RMS body speed from the same markers. Responses in healthy subjects and veterans were compared using repeated-measures ANOVA (within-subject factors: eyes open/closed, standing surface; between-subject factor: subject group).

Results: Under all conditions, the RMS displacement of the sacral marker was 2.3-4 times as large for the mTBI group. The group difference ($p<0.04$) and eyes open vs closed ($p<0.003$) were both significant. The findings were similar for trunk speed and also for motion of the neck marker. The greatest balance impairment was in mTBI veterans standing on foam with eyes closed. Postural stability in the mTBI group while standing on the hard floor with eyes open was similar to that in healthy subjects standing on foam with eyes closed.

Conclusions: Disequilibrium in veterans with a history of mTBI is associated with decreased postural stability, particularly under conditions that challenge the vestibular system. The clinical significance of these findings is that these individuals do not typically exhibit balance impairment during routine clinical examination. Our results suggest, however, that in a physically challenging combat environment, these individuals would be at risk for falls and further injury.

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The human translational vestibulo-ocular reflex in response to complex motion

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We studied the translational vestibulo-ocular reflex (tVOR) in four healthy human subjects during complex, unpredictable sum-of-sines head motion (combination of 0.73, 1.33, 1.93, and 2.93 Hz), while subjects viewed a target 15 cm away. Ideal eye velocity was calculated from recorded head motion; actual eye velocity was measured with scleral coils. The gain and phase for each frequency component was determined by least-squares optimization. Gain averaged approximately 40% and did not change with frequency; phase lag increased with frequency to a maximum of 66°. Fitting actual to ideal eye velocity predicted a tVOR latency of 48 m/s for vertical and 38 m/s for horizontal translation. These findings provide further evidence that the normal tVOR is considerably undercompensatory, even at low frequencies if the stimulus is not predictable. The similarity of this behavior to that of pursuit suggests that these two eye movements may share some aspects of neural processing.

Keywords: vestibular; otolith; translation; eye movements

Introduction

The translational vestibulo-ocular reflex (tVOR), driven by head acceleration signals from the otolith organs, generates eye movements to compensate for linear head motion. Prior work has shown that the human tVOR, unlike the rotational VOR (rVOR), only partially compensates for head movement: the evoked eye velocity is considerably less than what would be needed to maintain steady gaze on the target of interest. This is true regardless of viewing distance,[1] and it holds for both continuous sinusoidal translation and for abrupt steps of head velocity.[2,3] A recent study of vertical translation showed that for continuous 2 Hz stimulation, eye velocity is on average only about 60% of its ideal value.[1]

The reason that the gain of the tVOR is less than ideal is not clear. It has been pointed out that natural head motion often combines translations and rotations in such a way that the eye velocity re-

quired for gaze stabilization is reduced; thus it may not be functionally important that the tVOR gain is low.[3–5] Although this may be true, it is difficult to explain why the gain remains low even when there is no counteracting head rotation. An alternative hypothesis is that the tVOR is optimized for a function other than gaze stabilization, for example, for maximizing depth perception from motion parallax cues.[6]

To understand more fully the function of the tVOR, it is important to define its response over a wider range of stimuli. In the present study, we focused on the response to a complex motion stimulus consisting of a sum of nonmultiple sinusoids. Sum-of-sines stimuli have been used to study the behavior of other types of smooth eye movements, including pursuit[7] and the rVOR.[8] These stimuli are less predictable than single-frequency sinusoids, and they may better approximate the types of passive head motion that occur naturally.

Table 1. Stimulus characteristics for SOS translation[a]

Frequency (Hz)	Amplitude (cm)	Velocity (cm/s)	Acceleration (cm/s^2)	Phase (°)
0.73	1.0	4.6	21.0	0
1.33	1.0	8.34	69.8	0
1.93	1.0	12.13	147.1	0
2.93	1.0	18.4	338.9	0

[a]The SOS stimulus was a combination of four frequencies with equal displacement amplitudes, continued for 30 seconds. The same stimulus was used for both interaural and vertical translation.

Methods

Four neurologically normal adult subjects were studied. All gave signed informed consent under a protocol that was approved by the Institutional Review Board of the Louis Stokes Cleveland Department of Veterans Affairs Medical Center.

Subjects sat in a chair that was mounted on a motion platform (Moog 6DOF2000E, Moog, East Aurora, NY). The head was restrained by a helmet that was attached to the chair. Motion stimuli were preprogrammed and consisted of a combination of four sinusoidal oscillations (Table 1, Fig. 1). The same stimulus profile was used to test responses to vertical and interaural translation. Because the platform does not have a closed-loop controller, small differences between the specific and actual motion were possible; thus, all analysis was based on the recording of actual head motion. During translation, the subject was instructed to fixate a target that was located 15 cm from the eyes. The experimental room was fully illuminated. The tVOR was studied during fixation of a visible target, rather than in the dark or during intermittent fixation of a flashing target, because prior work has shown that under those conditions, tVOR gain is substantially reduced, even at frequencies beyond those at which visual tracking operates.[1,11]

Eye movements were measured using a magnetic-field scleral coil system. Each subject wore a dual coil (Skalar, the Netherlands) on each eye. Standard three-dimensional eye movement analysis methods were used to calculate instantaneous eye position. To account for incomplete coupling of the head to the platform, head motion was measured directly using a motion tracking system (Vicon Motion Systems, Los Angeles, CA) with infrared-reflective markers on the forehead and over the zygomatic processes. The measured head movement was used to calculate the ideal eye velocity for gaze stabilization based on the distance of the fixation target from the eyes. The details of the calibration of eye and head motion have been summarized previously.[1]

Data analysis was performed using custom programs in MATLAB and Python. For both ideal and measured eye velocity, the gain and phase of each of the four frequency components was determined using a least-squares optimization technique (scipy.optimize.leastsq, www.scipy.org), fitting data to the following function:

$$\omega = \sum_{i=1}^{4} g_{i*}\sin(2\pi f_i t + \varphi_i),$$

where w is the eye velocity, g_i are the gains (amplitudes) and ϕ_i the phases of the individual components. The gains and phases were the free parameters for the optimization. For measured eye velocity, the optimization process excluded saccades and fit the function to slow-phase velocity only. Saccades were detected based on eye acceleration and jerk.[9] Statistical comparisons were performed using repeated-measures ANOVA in R.

Results

A representative response from one subject is shown in Figure 2. Note that the amplitude of actual eye velocity is considerably lower and the response is delayed, compared to ideal velocity. Figure 3 shows the average gains and phases for the four subjects for each frequency component, as determined by the optimization algorithm. The main findings are (1) gain is constant across this frequency range, but eye velocity is only about 40% of the ideal velocity that would stabilize gaze; and (2) there is an increasing phase lag with frequency, up to about 66° at the highest frequency. There was a significant effect of frequency on phase ($P < 0.002$), but not on gain ($P > 0.13$).

A phase lag that increases with frequency with constant gain could reflect a fixed delay in the
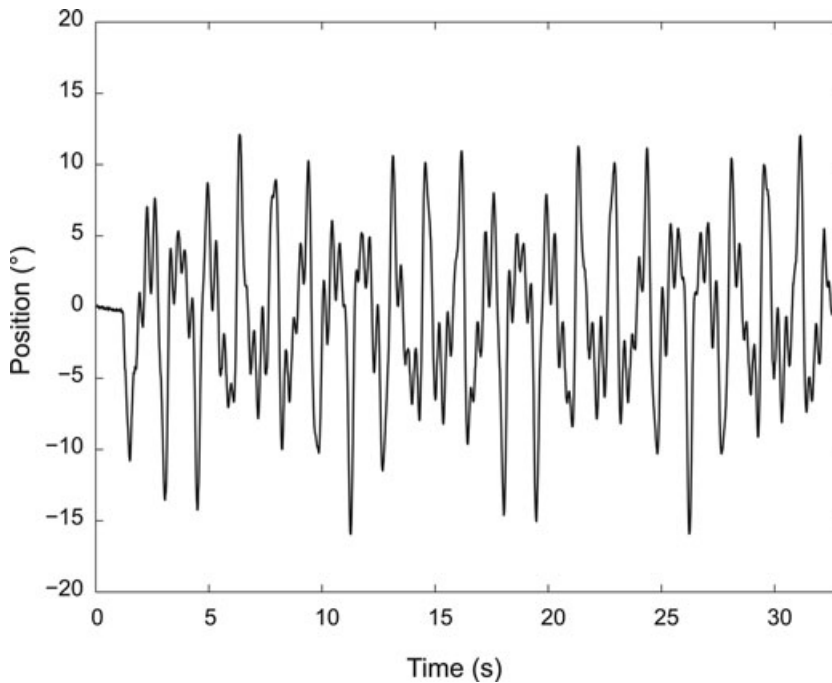
Figure 1. Sum-of-sines stimulus profile. The motion stimulus consisted of the sum of four sinusoids (Table 1) and had a total duration of 30 seconds. The same profile was used for both interaural and vertical platform motion. This figure depicts the calculated required right eye displacement for one subject, derived from Vicon recordings of head motion and target position relative to the orbit.

system. For each of the calculated phase values we determined the effective response latency:

$$\tau_i = \frac{\varphi_i}{f_i \times 360^\circ},$$

where τ_i is the response latency, ϕ_ι is the phase lag, and f_i is the frequency. Overall, combining frequencies, the estimated latency was 49 ± 10 m/s (mean $\pm$ 95% CI) for vertical translation and 27 ± 17 m/s for interaural translation.

Fitting actual eye velocity directly to scaled and delayed ideal eye velocity (Fig. 4) predicted similar latencies: 48 ± 13 m/s for vertical and 38 ± 7 m/s for interaural translation. To do this, a least-squares fit was performed for latency values from 2 to 100 m/s in 2 m/s increments (corresponding to 500 Hz sampling rate of eye velocity). For each subject and motion direction, the latency value that produced the lowest residual error was selected.

Finally, for each of the four subjects, we also recorded eye movements during single-frequency translation (both interaural and vertical) at 2 Hz. This allowed us to compare the gain and phase of the tVOR at 2 Hz with those of the SOS component that had nearly the same frequency (1.93 Hz). For simple sinusoidal motion, the gain was higher ($P < 0.05$) and the phase lag less ($P < 0.05$) than they were for the corresponding frequency of SOS translation (Table 2). On average, the gain was 32% lower in the SOS condition, and the phase lag was greater by 15°.

Discussion

In this study, we have investigated the human interaural and vertical tVOR in response to pseudo-random SOS translation, during fixation of a target in the light. Our data provide further evidence that the tVOR is not a simple linear reflex but is strongly influenced by the complexity of the motion that elicits it. The principle of superposition does not hold because both the gain and phase of the 2 Hz component of a SOS stimulus are different from those of a simple 2 Hz translation. In fact, although the response is undercompensatory for single-frequency movement,[1] it is even more so for SOS translation, at the same viewing distance and under the same
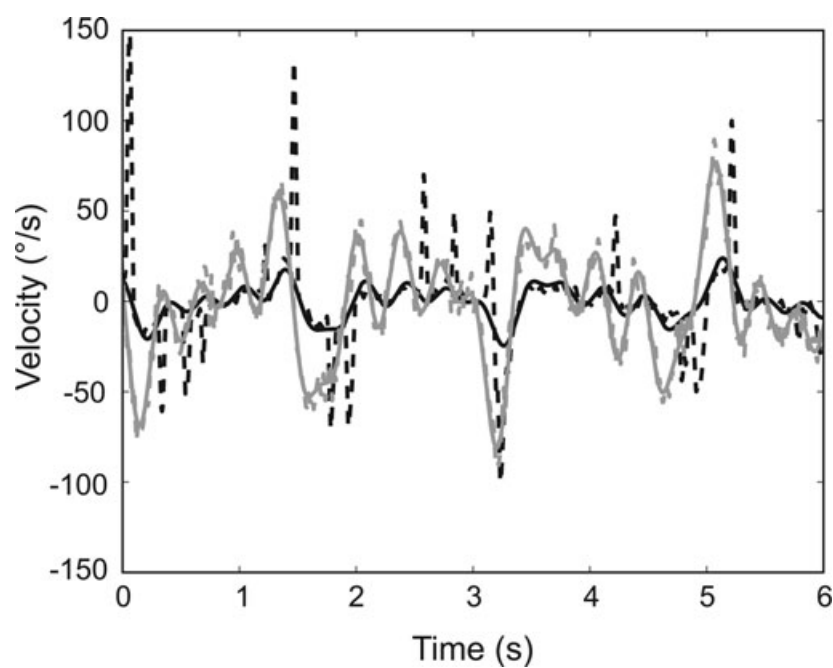
Figure 2. Representative response to SOS vertical translation in one subject, showing both ideal and actual eye velocity. The dashed lines depict the calculated (ideal) or measured (actual) velocities. The solid lines show the results of the corresponding SOS fits.

visual conditions (Table 2). Other studies have tested the single-frequency tVOR over a range of frequencies.[10,11] For single-frequency translation, the gain decreases with increasing frequency, and the phase lag increases less steeply than we have found here for SOS translation. These findings suggest that simple sinusoidal motion may evoke an additional predictive mechanism that is able to increase eye velocity to enhance the response, but when predictability is reduced by a more complex stimulus, gain is lower and response delay is increased.

**Table 2. Comparison of tVOR with single-frequency (2 Hz) and SOS translation (1.93 Hz component)[a]**

	2 Hz single-frequency	1.93 Hz SOS component
Horizontal gain	0.58 ± 0.13	0.41 ± 0.19
Horizontal phase	$-13 \pm 4°$	$-23 \pm 11°$
Vertical gain	0.48 ± 0.21	0.36 ± 0.11
Vertical phase	$-15 \pm 8°$	$-35 \pm 12°$

[a]The single-frequency tVOR had a higher gain and smaller phase lag than the corresponding frequency component from SOS translation.

Our findings, in combination with prior work, raise several important questions regarding the tVOR. First, what is the functional anatomy of the human tVOR, that is, what brain regions are responsible for different aspects of tVOR behavior, including prediction? Second, how do these findings regarding the tVOR relate to those for other types of smooth eye movements (e.g., pursuit, rVOR)? Third, what is the most appropriate stimulus with which to characterize and quantify the behavior of the tVOR and to assess clinical disorders affecting this reflex? Finally, how does the stimulus specificity of tVOR gain and phase inform our understanding of its function and purpose? In general, these questions cannot be easily answered with currently available data and will require further study, but several points can be made.

Comparison of tVOR to rVOR and pursuit

Our findings for the tVOR distinguish it from the rVOR, for which the SOS gains differ little from those during single-frequency rotation under normal visual conditions; only when visual-vestibular conflict is imposed, such as by changes in magnification, is a notable effect of stimulus predictability
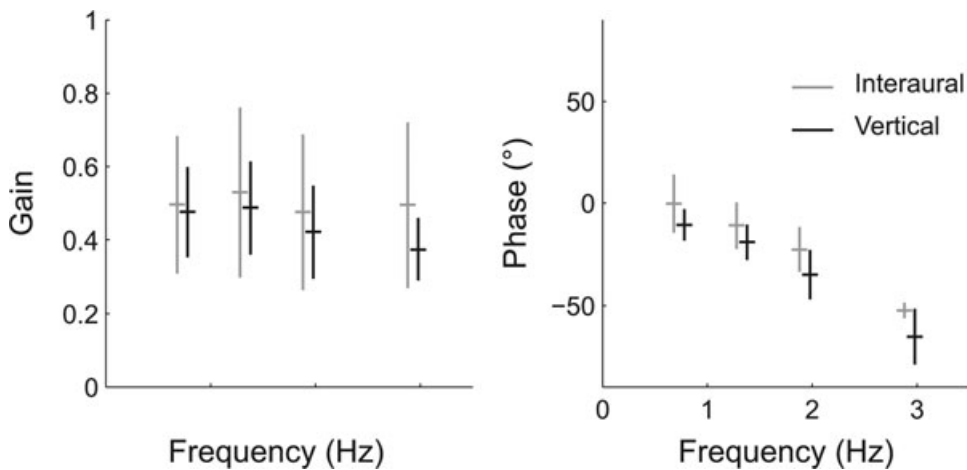
Figure 3. Frequency response of tVOR for SOS stimulus. The gain and phase corresponding to each of the four frequency components is shown for both interaural and vertical translation (mean ± 95% CI).

apparent.[12] In this sense, perhaps, the rVOR is more purely a vestibular reflex than is the tVOR.

On the other hand, the tVOR results are very similar to the behavior of foveal pursuit. Pursuit gain is higher and eye and stimulus motion are more nearly in phase for single-frequency, predictable target motion, than during SOS pursuit. Similar to pursuit, tVOR gain is constant across frequencies during SOS translation, and the phase lag increases steadily with frequency, although shifted toward higher frequencies. One explanation of these findings is that visual tracking and the tVOR share neural processing with respect to motion prediction but that the shorter latency of the otolith inputs in comparison to visual motion signals allows the tVOR to operate at higher frequencies than pursuit. In the case of pursuit, it has also been shown that the highest frequency component sets the gains for the other response components.[7] Further study will be required to determine if this is true for the tVOR.

Their behavior with respect to stimulus predictability is only one of several similarities between pursuit and the tVOR. In terms of visual function, both generally act (at least partially) to stabilize the image of an object of regard at the expense of background motion. They also have similar kinematics with respect to Listing's Law,[13,14] and they share a dependence on the cerebellum; complete cerebellar lesions abolish both pursuit[15,16] and the tVOR.[17–19]

Latency of the tVOR

Prior studies have found that the tVOR has a longer latency than the rVOR, perhaps reflecting its additional computational complexity and the lack of a simple brainstem pathway (analogous to the "three-neuron arc" of the rVOR) that can generate a response independent of higher-order processing. The extent to which tVOR latency is prolonged is uncertain, however, as latencies from as little as 18 m/s up to as much as 50 m/s have been reported.[3,20–23] These studies determined latency based on the initiation of eye movement in response to abrupt interaural translations; a challenge to this technique is that it depends on the method by which the onset of motion is determined. Thus, differences in these methods and recording techniques may account for some of the variability of the measures.

Our data from sustained unpredictable translations offer another means to estimate tVOR latency, namely by determining the time shift that provides the best fit (with the appropriate scaling) between head and eye velocity. By this method, we found average latencies of 48 s for vertical and 38 s for interaural translation, the latter well within the range of previously reported values. The slightly longer latency for vertical translation could indicate an increased processing delay for saccular signals or for the vertical eye movements that they evoke; further study will be needed to verify this finding.
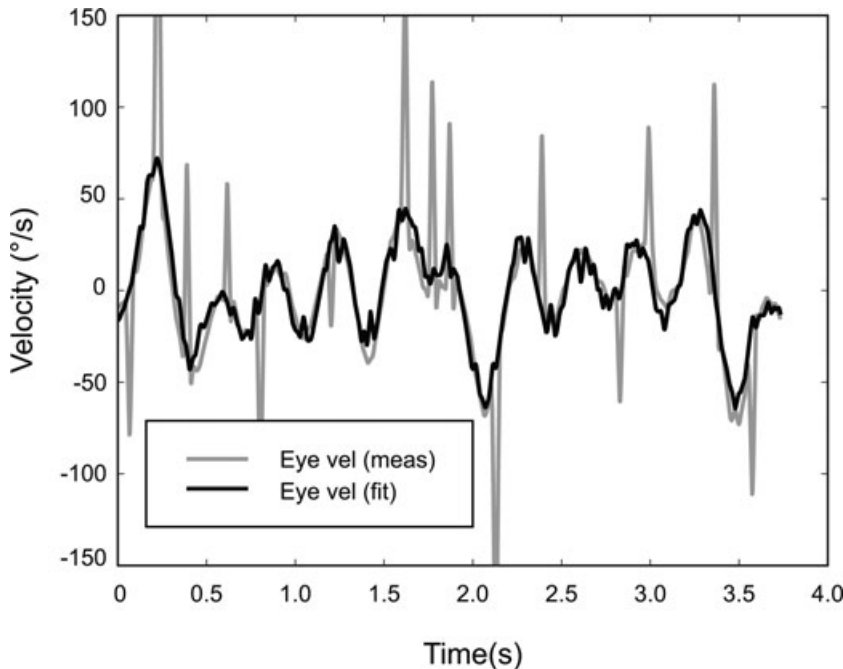
Figure 4. Least-squares fit of recorded to ideal eye velocity. The measured eye velocity was fit to the calculated required eye velocity, with the scale factor as the free parameter. The fit was performed for a range of time shifts (see text). The time shift (latency) with the lowest residual error was chosen, and the results are depicted here for one subject (vertical translation).

Functional anatomy and clinical implications

The functional anatomy of the otolith-driven vestibular reflexes has been best studied for the static otolith ocular reflex, namely ocular counter roll and the pathologic ocular tilt reaction. The brainstem and cerebellar network underlying this reflex has been carefully elucidated.[24,25] Less is known, however, regarding the neuroanatomy and clinical disorders of the tVOR. As noted above, humans with diffuse cerebellar disease lose the tVOR completely.[17–19] This is distinctly different from the rVOR, which is generally preserved in cerebellar disease, although its gain and/or direction may be altered. Within the cerebellum, the nodulus and uvula have been shown to play a role in several aspects of otolith signal processing, including the integration of head acceleration[26] and the disambiguation of linear acceleration signals related to tilt and translation.[27] Whether a similar segregation of function among cerebellar areas occurs in humans, remains to be determined. Furthermore, the similarity of tVOR behavior to that of pursuit and the likely role of predictive mechanisms suggest that other brain areas, such as motion processing areas of the cerebral cortex, may play an important role in the tVOR.

Acknowledgments

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Liao, K., M.F. Walker, A. Joshi, *et al.* 2008. Vestibulo-ocular responses to vertical translation in normal human subjects. *Exp. Brain Res.* **185:** 553–562.
2. Crane, B.T., J. Tian, G. Wiest, *et al.* 2003. Initiation of the human heave linear vestibulo-ocular reflex. *Exp. Brain Res.* **148:** 247–255.
3. Ramat, S. & D.S. Zee. 2003. Ocular motor responses to abrupt interaural head translation in normal humans. *J. Neurophysiol.* **90:** 887–902.
4. Crane, B.T. & J.L. Demer. 1997. Human gaze stabilization during natural activities: translation, rotation, magnification, and target distance effects. *J. Neurophysiol.* **78:** 2129–2144.
5. Imai, T., S.T. Moore, T. Raphan, *et al.* 2001. Interaction of the body, head, and eyes during walking and turning. *Exp. Brain Res.* **136:** 1–18.

6. Liao, K., M.F. Walker, A. Joshi, *et al*. 2008. A reinterpretation of the purpose of the translational vestibulo-ocular reflex in human subjects Prog. *Brain Res.* **171:** 295–302.

7. Barnes, G.R., S.F. Donnelly & R.D. Eason. 1987. Predictive velocity estimation in the pursuit reflex response to pseudo-random and step displacement stimuli in man J. *Physiol.* **389:** 111–136.

8. Han, Y.H., A.N. Kumar, M.F. Reschke, *et al*. 2005. Vestibular and non-vestibular contributions to eye movements that compensate for head rotations during viewing of near targets. *Exp. Brain Res.* **165:** 294–304.

9. Wyatt, H.J. 1998. Detecting saccades with jerk. *Vision Res.* **38:** 2147–2153.

10. Paige, G.D., L. Telford, S.H. Seidman, *et al*. 1998. Human vestibuloocular reflex and its interactions with vision and fixation distance during linear and angular head movement. *J. Neurophysiol.* **80:** 2391–2404.

11. Liao, K., R.J. Leigh & M.F. Walker. 2009. The frequency response of the human translational vestibulo-ocular reflex [abstract]. 2009 Neuroscience Meeting Planner. Program No. 760.6.

12. Demer, J.L. 1994. Effect of aging on vertical visual tracking and visual-vestibular interaction. *J. Vestib. Res.* **4:** 355–370.

13. Angelaki, D.E., H.H. Zhou & M. Wei. 2003. Foveal versus full-field visual stabilization strategies for translational and rotational head movements. *J. Neurosci.* **23:** 1104–1108.

14. Walker, M.F., M. Shelhamer & D.S. Zee. 2004. Eye-position dependence of torsional velocity during interaural translation, horizontal pursuit, and yaw-axis rotation in humans. *Vision Res.* **44:** 613–620.

15. Westheimer, G. & S.M. Blair. 1973. Oculomotor defects in cerebellectomized monkeys. *Invest. Ophthalmol.* **12:** 618–621.

16. Zee, D.S., R.D. Yee, D.G. Cogan, *et al*. 1976. Ocular motor abnormalities in hereditary cerebellar ataxia. *Brain.* **99:** 207–234.

17. Wiest, G., J.R. Tian, R.W. Baloh, *et al*. 2001. Otolith function in cerebellar ataxia due to mutations in the calcium channel gene CACNA1A. *Brain.* **124:** 2407–2416.

18. Zee, D.S., M.F. Walker & S. Ramat. 2002. The cerebellar contribution to eye movements based upon lesions: binocular three-axis control and the translational vestibulo-ocular reflex. *Ann. N. Y. Acad. Sci.* **956:** 178–189.

19. Liao, K., M.F. Walker & R.J. Leigh. 2008. Abnormal vestibular responses to vertical head motion in cerebellar ataxia. *Ann. Neurol.* **64:** 224–227.

20. Bronstein, A.M. & M.A. Gresty. 1988. Short latency compensatory eye movement responses to transient linear head acceleration: a specific function of the otolith-ocular reflex. *Exp. Brain Res.* **71:** 406–410.

21. Gianna, C.C., M.A. Gresty & A.M. Bronstein. 1997. Eye movements induced by lateral acceleration steps. Effect of visual context and acceleration levels. *Exp. Brain Res.* **114:** 124–129.

22. Tian, J.R., B.T. Crane, G. Wiest, *et al*. 2002. Effect of aging on the human initial interaural linear vestibulo-ocular reflex. *Exp. Brain Res.* **145:** 142–149.

23. Crane, B.T., J. Tian, G. Wiest, *et al*. 2003. Initiation of the human heave linear vestibulo-ocular reflex. *Exp. Brain Res.* **148:** 247–255.

24. Brandt, T. & M. Dieterich. 1994. Vestibular syndromes in the roll plane: topographic diagnosis from brainstem to cortex. *Ann. Neurol.* **36:** 337–347.

25. Baier, B., S. Bense & M. Dieterich. 2008. Are signs of ocular tilt reaction in patients with cerebellar lesions mediated by the dentate nucleus? *Brain.* **131:** 1445–1454.

26. Walker, M.F., J. Tian, X. Shan, *et al*. 2010. The cerebellar nodulus/uvula integrates otolith signals for the translational vestibulo-ocular reflex. PLoS One. **5:** e13981.

27. Yakusheva, T., P.M. Blazquez & D.E. Angelaki. 2008. Frequency-selective coding of translation and tilt in macaque cerebellar nodulus and uvula. *J. Neurosci.* **28:** 9997–10009.